LETTERS TO THE EDITOR

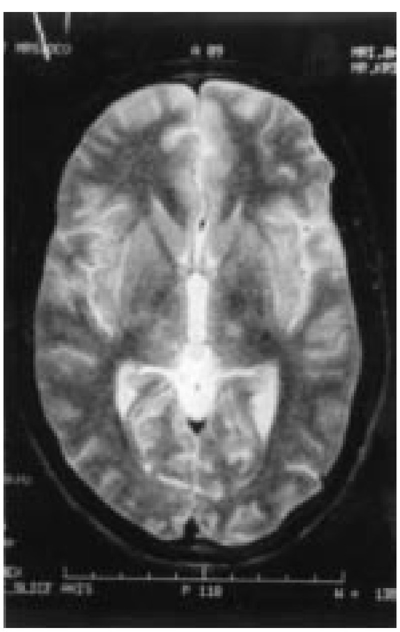
Cerebellar ataxia due to lead encephalopathy in an adult

Lead has been used by humans as long as recorded history for various purposes ranging from jewellery to weapons and construction materials, paints, and pigment manufacture. Lead colic was known to ancient physicians since the time of Hippocrates, but encephalopathy was first described as late as 1925; it is especially common in children. Here we report a rare case of lead encephalopathy associated with ataxia in a 30 year old battery plate manufacturer.

He had been working for the past 12 years in a factory making battery plates. He presented with history of abnormal behaviour and unsteadiness of gait for 8 days accompanied by colicky abdominal pain and paraesthesiae in the legs. Later the patient started behaving abnormally; he shouted irrelevantly, became violent, and refused to recognise relatives. He was treated with antipsychotic medication which quietened him. Two days later he had difficulty in walking. His gait was unsteady and speech was incoherent.

Enquiry disclosed two earlier episodes of abdominal pain with abnormal behaviour in the past year which responded to treatment, the details of which were not available. Two other factory workers had also had episodic abnormal behaviour but were not available for interrogation. There was no history of fever or symptoms suggestive of raised intracranial pressure, seizures, or focal motor or sensory deficits. The patient denied consumption of alcohol on a regular basis.

On admission the patient was afebrile, pulse 82/min, BP 116/76 mm Hg. There was mild pallor and a suspicious bluish grey discoloration of the gums. He was conscious and oriented, but extremely restless. He was totally anarthric. A detailed evaluation of higher functions was not possible due to the restlessness and anarthria, but from the limited evaluation, comprehension appeared intact. There was no evidence of hallucinations or delusions. The optic fundi were normal. There was no nystagmus and the lower cranial nerves were normal except for slow movements of the tongue.



T2 weighted MRI showing hyperintensities in both thalami.

Motor system examination disclosed no significant weakness. There were prominent cerebellar signs in the form of truncal ataxia, impaired finger to nose and knee-heel tests, and dysdiadochokinesia. There was no tremor and no sensory deficits. Deep tendon reflexes were normal. Both plantar reflexes were extensor. There was no neck stiffness.

The history of abdominal colic and behavioural abnormalities in a person working with battery plates and also of similar complaints in coworkers, raised a clinical suspicion of lead toxicity.

Blood lead concentration estimated on the next day was 89 μg/dl (normal range 10–15 μg/dl), which confirmed lead toxicity. The patient had hypochromic microcytic anaemia (Hb 8.3 g). There was no basophilic stippling. Urine examination was normal and negative for porphyrins. There was no azotaemia (BUN 10.0 mg/dl, serum creatinine 1.0 mg/dl), Serum electrolytes were normal Na 133 (normal 132-–144) meq/l, K 4.6 (3.6–5.0) meq/l, Cl 98 (96–108) meq/l, Ca 10.0 (9-ll) mg/dl. Liver function tests were normal.

T2 weighted MRI disclosed bilateral hyperintense lesions in both thalami (figure). The EEG did not show any focal or background rhythm abnormalities. Peripheral nerve conduction studies were within normal limits.

The patient was treated with mannitol and intravenous fluids. Oral chelation therapy was started with penicillamine on day 2. EDTA or dimercaprol could not be instituted due to unavailability. The patient showed significant improvement in behaviour, and speech returned by day 3 of admission, although extremely slurred. The unsteadiness and dysarthria improved steadily until discharge 2 weeks later. Repeat estimation of lead concentration at discharge was 64 μg/dl. The patient showed complete neurological recovery on follow up 6 months after discharge. He was able to perform his routine duties, but decided to look for a different job. A repeat blood lead concentration was 52 g/dl.

Lead intoxication most often occurs in 1 to 3 year old children due to chewing of lead paint. Acute encephalopathy is a serious complication in children, which can be fatal or leave permanent neurological sequelae.[1]

Lead toxicity is much less common in adults. It is mainly an occupational hazard due to inhalation of lead fumes or physical contact with lead in processes that require remelting of lead, such as painting, lead smelting, pottery glazing, and storage battery manufacture. The emissions of vehicles using leaded petroleum is a recognised source of environmental pollution in urban areas.[2] The usual manifestations of lead poisoning in adults are colic, anaemia, and peripheral motor neuropathy. Encephalopathy is rare. Whitfield *et al* (1972) reported the largest series of 23 adults with lead encephalopathy; all these followed consumption of illicit liquor contaminated by lead (moonshine).[3] Ten of these patients had altered sensorium; 18 of them had seizures. Other symptoms included dizziness, syncope, disorientation, and blindness. One had papilloedema. None of the patients had ataxia. Ataxia was a prominent feature in our patient and has been described as a feature of lead encephalopathy in children.[1 4] This could be secondary to raised intracranial pressure or to direct involvement of the cerebellum. Lead acts as a cellular toxin by inhibiting mitochondrial respiration. The increased resistance of the adult to encephalopathy and ataxia is believed to be due to the capacity of the mature brain to sequestrate lead away from its mitochondrial site of action within the cerebral and cerebellar neurons.[5]

T2 weighted MRI in our patient disclosed hyperintensities in both thalami (figure). Schroter *et al* reported high signal intensities in the periventricular white matter, basal ganglia, insula, posterior thalamus, and pons.[6]

Our patient did not have basophilic stippling of peripheral red blood cells. Basophilic stippling of erythrocytes is reported in 91% of patients by Whitfield *et al*,[3] but was seen in only 40% of cases reported by Greengard *et al*.[4] It is more pronounced in the bone marrow than in the peripheral blood[7] and may be missed unless carefully looked for.

The extent of clinical recovery was out of proportion to the decline in blood concentrations. Free erythrocyte protoporphyrin and the urinary concentrations of γ-aminolevulinic acid (ALA) or coproporphyrin are better clinical correlates of lead toxicity, rather than estimations of blood lead concentration. In our patient only the urinary porphobilinogen could be estimated.

Severe medical illness, alcohol, dehydration, and emotional stress are known to precipitate symptoms of lead poisoning, but we were unable to identify any such factors in our patient.

To summarise, frank encephalopathy due to lead intoxication has become increasingly rare in adults. We report a patient with lead encephalopathy who presented with behaviour problems and cerebellar ataxia.

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"All tibial foot" with sensory crossover innervation between the tibial and deep peroneal nerves

One of the most common and well studied innervation anomalies in the upper limbs is the Martin-Gruber anastomosis.[1 2] In the lower limbs, the anomaly is uncommon except for the accessory deep peroneal nerve.[1 2] Recently, an exclusive innervation of the extensor digitorum brevis by the tibial nerve, "all tibial foot" has been reported.[3-5] We experienced a similar patient with "all tibial foot", who, in addition, showed sensory anomaly.

A 23 year old man with encephalitis had nerve conduction studies (NCSs) to exclude coexistent peripheral neuropathy. The studies were normal except for the anomalous innervation in the bilateral lower limbs. Peroneal nerve stimulation at the ankle, fibular head, and popliteal fossa elicited only a negligible compound muscle action potential (CMAP) over the extensor digitorum brevis. The accessory deep peroneal nerve was not demonstrated by stimulation behind the lateral malleolus.[1 2] A normal CMAP from the extensor digitorum brevis was elicited by stimulating the tibial nerve at the ankle and popliteal fossa (figure A). Although CMAP of the anterior tibial muscle was normally elicited by stimulating the common peroneal nerve at the fibular head, a small CMAP was recorded also by the stimulation of the tibial nerve at the popliteal fossa (figure B).

Sensory studies of the sural, superficial peroneal and medial plantar nerves were normal. Stimulation of the deep peroneal nerve at the ankle gave rise to a normal antidromic sensory nerve action potential (SNAP) in the skin between the first and second toes, where an obvious SNAP was recorded even after the stimulation of the tibial nerve behind the medial malleolus (figure C).

Our patient had "all tibial foot" for the motor innervation, the anomalous dual innervation of the anterior tibial muscle, and the sensory coinnervation of the skin between the first and second toes by the tibial and deep peroneal nerves. Findings were similar on both sides. We speculate that, in our patient, the deep peroneal nerve becomes almost pure sensory after branching motor fibres for the anterior tibial muscle, and that the extensor digitorum brevis is innervated by the tibial nerve. Further, the tibial nerve had a motor branch for the anterior tibial muscle and a sensory branch to supply the area typically innervated by the deep peroneal nerve. Although rare, we should keep in mind this anomaly in the practice of nerve conduction studies.

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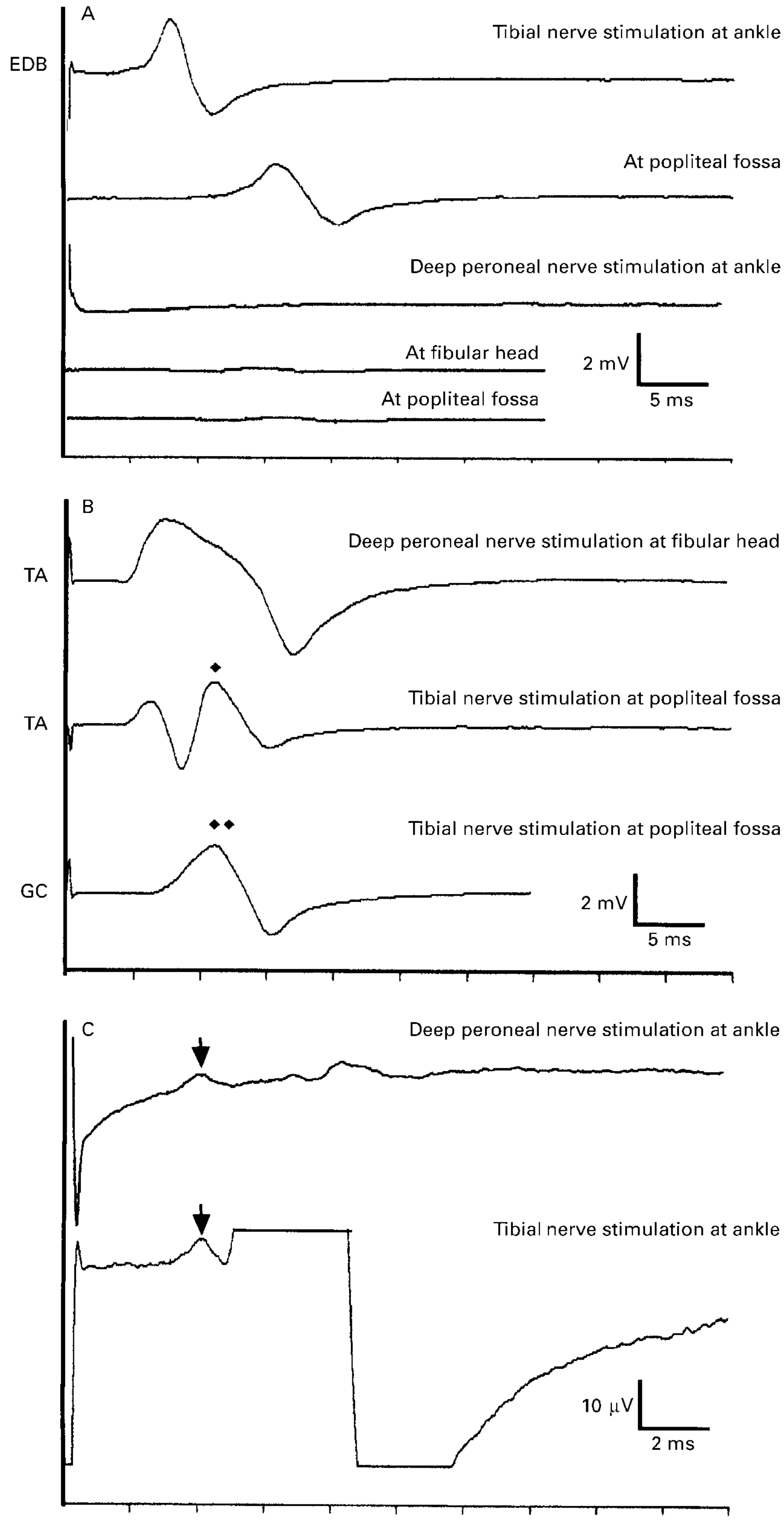

(A) Stimulation of the tibial and deep peroneal nerves at the ankle and popliteal fossa. Recordings from the extensor digitorum brevis. (B) Stimulation of the tibial and deep peroneal nerves at the popliteal fossa. Recordings from the anterior tibial muscle. The second negative peak (◆) is probably made by the volume conduction from the simultaneously contracting gastrocnemius muscle (◆◆). (C) Stimulation of the tibial and deep peroneal nerves at the ankle. In either case, sensory nerve action potential (arrow) was recorded from the skin between the first and second toes.

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IgG Anti-GT1a antibodies which do not cross react with GQ1b ganglioside in a pharyngeal-cervical-brachial variant of Guillain-Barré syndrome

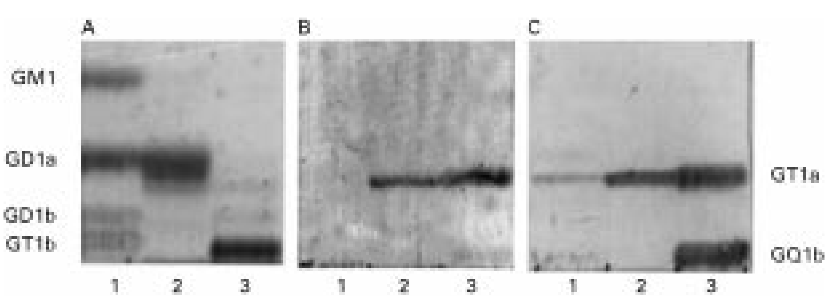
IgG anti-GT1a antibody which cross reacts with GQ1b ganglioside is associated with ophthalmoplegia in Guillain-Barré syndrome and in Fisher's syndrome, a variant of Guillain-Barré syndrome.[1] Pharyngeal-cervical-brachial weakness is another regional variant of Guillain-Barré syndrome originally described by Ropper.[2] Its symptoms resemble those of botulism and diphtheria and are characterised by marked oropharyngeal, neck, and shoulder weakness with areflexia only in the arms. We report on a patient with this variant who had high titres of serum IgG anti-GT1a antibody which did not cross react with GQ1b.

A 55 year-old woman was admitted due to sudden onset ptosis, trouble with swallowing, and nausea and vomiting. One week before admission she had had an upper respiratory infection with diarrhoea which lasted for several days. On admission, dilated pupils and ocular paralysis were noted. Fever of up to 40°C lasted for a week. Her neurological symptoms were at their worst on day 5. At that time, she was alert but could not open or move her eyes or swallow anything. Her pupils were dilated with sluggish light reflexes. The tip of her tongue did not protrude from her mouth. The Medical Research Council grades for the facial muscles ranged from 3 to 4; neck flexion and extension were graded 2; the deltoid and the biceps brachii and triceps muscles 4. Muscle strength in the lower limbs was normal. Deep tendon reflexes were absent in all the limbs, and the Babinski sign was negative. There was no sensory disturbance or cerebellar ataxia. She complained of headache, nausea, and vertigo on turning her head, but no meningeal signs were present. Her white blood cell count (15 600/μl) and serum C-reactive protein (9.0 mg/dl) were raised. Routine laboratory findings for liver and renal functions were normal. On day 5 her CSF had a raised protein concentration of 80 mg/dl, and cells were 7/μl. Motor conduction velocity in the right tibial nerve on Day 11 was slightly reduced (37 m/s), whereas the motor and sensory conduction velocities in the right medial nerve were normal. A stool culture was negative for *Campylobacter jejuni*. Botulism and diphtheria were excluded because her neurological symptoms occurred a week after the onset of diarrhoea. Results of the nerve conduction and CSF studies showed abnormal values.Guillain-Barré syndrome was diagnosed. A daily intramuscular injection (8 mg/day) of dexamethasone was given for 3 days then tapered off over the next 20 days. Two weeks after admission, her internal ophthalmoplegia and dysphagia had disappeared. One month later, ocular movements were almost normal, ptosis remained only in the right eye, the strength of the neck muscles had increased to 4, and deep reflexes became detectable. All these symptoms disappeared within 3 months of onset.

Serum antiganglioside antibody titres were determined using an enzyme linked immunosorbent assay (ELISA). On day 11, the titres of anti-GM1, GM2, GD1a, GD1b IgG, and IgM antibodies were <500; whereas the titre of the IgG anti-GT1a antibody had increased to 16 000 and that of the anti-GQ1b antibody was 500 (normal ranges were set at <500). No IgM antibodies to GT1a or GQ1b were detected. Thin layer chromatography with immunostaining confirmed that her serum IgG reacted with GT1a but not with GQ1b or GD1a (figure). An absorption study showed that her IgG anti-GT1a antibodies were not absorbed by GQ1b, GD1a, or GM1 (data not shown). Three months after onset, the respective serum titres of the anti-GT1a and anti-GQ1b IgG antibodies had decreased to 500 and <500.

The regional distribution of her symptoms was the same as that of the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome, except for the areflexia of the legs. Based on clinical observations of three patients, Ropper[2] described this variant as sparing the power and reflexes in the legs. One of his patients, however, had generalised areflexia. We therefore classified our patient as having the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome. Her headaches, nausea, and vertigo suggest the involvement of a central component.

Serum antiganglioside antibodies are present in patients with Guillain-Barré syndrome. Some of these antibodies are associated with certain clinical variants or signs of this syndrome. Chiba *et al*[1] detected IgG anti-GT1a and anti-GQ1b antibodies in most of a group of patients with Fisher's syndrome or Guillain-Barré syndrome with ophthalmoplegia and showed that the anti-GT1a antibodies in these patients cross reacted with GQ1b. Our patient with the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome also had increases in IgG anti-GQ1b and anti-GT1a antibodies that paralleled the clinical course. The anti-GT1a antibody titre in our patient, however, was much higher than the anti-GQ1b antibody titre; moreover, the anti-GT1a antibody did not cross react with GQ1b. Mizoguchi *et al*[3] also detected IgG anti-GT1a antibodies which did not cross react with GQ1b, as well as anti-GD1a antibodies in the serum of a patient with this Guillain-Barré syndrome variant. Furthermore, O'Leary *et al*[4] reported IgG anti-GT1a and anti-GQ1b antibodies in three patients with acute oropharyngeal palsy. The presense of IgG anti-GT1a antibodies in these patients and in ours was associated with the emergence of acute polyneuropathy with marked lower cranial nerve involvement. IgG anti-GT1a antibodies which do not cross react with GQ1b may be closely related to the proclivity of Guillain-Barré syndrome to manifest oropharyngeal palsy or to the cause of its pharyngeal-cervical-brachial variant. The IgG anti-GT1a antibody present in Fisher's syndrome may recognise a structure common to GT1a and GQ1b gangliosides,[1] whereas in the pharyngeal-cervical-brachial variant it would react with another epitope specific to GT1a.



Thin layer chromatography with immunostaining. Thin layer chromatography plates stained with (A) orcinol/sulphuric acid for hexose; (B) IgG from our patient, subsequently stained by peroxidase conjugated antihuman IgG antibodies; (C) IgG from a patient with Bickerstaff's brain stem encephalitis. Lane 1: bovine brain ganglioside mixtures. Lane 2: the GD1a and GT1a fraction separated from bovine brain ganglioside mixtures by Q-sepharose column chromatography. Lane 3: fraction enriched with GT1a and GQ1b. The plates were developed with C-M-0.2% calcium chloride in water (5:4:1 by volume).

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Dexamethasone is not necessarily unsafe in primary supratentorial intracerebral haemorrhage

Controversy surrounds the role of steroids in the treatment of intracerebral haemorrhage.[1] Theoretically, the short term use of dexamethasone is justified because it lessens the damaging effects of cerebral oedema, decreases intracranial pressure, and strengthens the blood-brain barrier. However, the possible benefit has to be weighed against the risk of complications, especially infections and gastrointestinal haemorrhage.[2]

So far, only two randomised, controlled trials concerning this controversy have been reported. One trial of 40 patients assumed to have intracerebral haemorrhage, found no beneficial effects of steroids.[3] However, this study had 22 patients with haemorrhagic infarcts or posterior fossa haemorrhage, and the outcome measures used had little clinical relevance regarding functional ability of the patients. The other trial, from Thailand,[4] was well designed, but had to be terminated prematurely after an interim analysis disclosed lack of benefit and presence of clinically important adverse effects. Patients in the dexamethasone group had more frequent infections, gastrointestinal haemorrhage, and diabetogenic effect, than the placebo group. There was a possible longer early survival in a subgroup with less severe stroke. Good recovery was noted in 17% of patients in the dexamethasone group, compared with 10% of patients in the placebo group, giving a difference of 7% in favour of the dexamethasone group.

In our experience, the complication rates are not as high with dexamethasone as reported by Poungvarin *et al*.[4] To consider the issue of safety of dexamethasone in primary supratentorial intracerebral haemorrhage, we undertook a double blind, randomised, placebo controlled trial as a pilot project.

Twenty six patients in the age group 40–80 years, with primary supratentorial intracerebral haemorrhage confirmed by brain CT, presenting within 5 days of onset were included. Patients with a history of previous disabling stroke or contraindications to steroid treatment were excluded. Informed consent was taken from relatives of all patients before admission into the trial. Dexamethasone was given intravenously, at a dose of 4 mg 6 hourly for 12 days, followed by 4 mg 12 hourly for two days and 2 mg 12 hourly for 2 days. Placebo injections of saline were given in the same dosage, from ampoules of similar size and shape, and with comparable labels, filled with a colourless solution indistinguishable from dexamethasone. No one involved with the study knew whether a particular patient was receiving dexamethasone or placebo. All patients received injectable ranitidine, 50 mg 8 hourly, for the period of the trial. The remainder of patient care was specified by their attending neurologist. The allocated treatment was stopped if the attending neurologist thought that the patients had developed a complication likely to be caused by, or aggravated with dexamethasone. No other antioedema measure (mannitol/glycerol) or neurosurgical intervention was undertaken, except in one patient who was found to have a ruptured anterior communicating artery aneurysm, diagnosed after randomisation.

Details of history and physical examination conducted at the time of admission were recorded. Haematoma size was calculated using the formula given by Kothari *et al*.[5] Outcome measures of all patients were assessed by one of us (PD), using the Glasgow outcome scores[6] at day 7 and at discharge. Fasting blood sugar was done one week after starting the treatment, to detect any diabetogenic effect. The development of fever after entry into the study was considered to be indicative of infection, irrespective of whether the focus of infection was detected or not. Statistical methods used were χ^2 test with continuity correction for categorical variables and a two tailed *t* test for continuous data.

The clinical characteristics, complications, and outcome of the patients are shown in the table. Both groups were well matched for age, hours from haemorrhage to treatment, blood pressure, volume and location of haematoma, and presence of intraventricular extension of blood. However, there were more comatose patients (Glasgow coma scale score<7) in the dexamethasone group (5/12) than in the placebo group (3/14).

The complication rates were higher in the placebo group than in the dexamethasone group (placebo group, 10 *v* dexamethasone group, 4), but the difference was non-significant. One patient in each group was found to be non-eligible after randomisation, and their allocated treatment was stopped within 3 days, but they continued to remain in the allocated group for analysis.

In all, seven patients died (five patients in the dexamethasone group died due to herniation within the first week and two patients in the placebo group died; one died of herniation in the first week, and the other died due to septicaemia on day 36). There was no difference between the groups in the number of patients who had a good outcome (2/12 in the dexamethasone group *v* 2/14 in the placebo group).

There could be many reasons why Poungvarin *et al*[4] found a higher frequency of adverse effects due to dexamethasone. Firstly, it may have been a chance finding. If they had continued the study further, the placebo group may have had similar complications such as infections or hyperglycaemia, thereby making the difference between the two groups non-significant. Secondly, the dexamethasone group may have had a higher proportion of serious patients who are more likely to develop complications such as infections, gastrointestinal haemorrhage, or hyperglycaemia. This may occur despite stratified randomisation, particularly when the numbers are few in the individual stratum. Arguably, similar factors in our placebo group may explain our findings. This may be true, but it emphasises the few and hence not very reliable data on whether dexamethasone is too unsafe to be used.

We conclude that dexamethasone in the regimen used in our trial is not likely to produce an unacceptably high rate of adverse effects in patients with primary supratentorial intracerebral haemorrhage. Whether or not dexamethasone or other corticosteroids are beneficial in this setting needs further study. The study by Poungvarin *et al*,[4] points to a higher proportion of patients making complete recovery by the 21st day in the treatment group (odds ratio 0.7, 95% CI, 0.2–2.4), this needs to be either confirmed or refuted.

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Clinical characteristics, complications, and outcome of patients

	Dexamethasone (n=12)	*Placebo (n=14)*
Age (mean (SD))	58.3 (11.7)	59.8 (7.4)
Haemorrhage to treatment (h, mean (SD))	30.3 (31.8)	27.2 (29.7)
Glasgow coma scale scores:		
3–7	5	3
8–11	2	6
12–14	5	5
Volume of haematoma (ml, mean (SD))	34 (36.4)	35.7 (35.3)
Location of haematoma:		
Basal ganglia	7	8
Thalamus	3	3
Lobar	2*	3†
Intraventricular leakage of blood	8	8
Mean (SD) arterial pressure (mm Hg)	123.9 (13.9)	133.8 (20.2)
Complications:		
Infections‡	3	7
Gastrointestinal bleeding§	0	2
Diabetogenic effect¶	1	1
Reasons for stopping allocated treatment:		
Gastrointestinal bleed	0	2
Abdominal distension	0	1
Jaundice	0	1
Wrong diagnosis	1	1
Outcome at discharge:		
Death		
Due to herniation	5	1
Due to infection	0	1
Vegetative	0	1
Dependent	5	9
Independent	2	2

* One patient had haemorrhagic infarct. †One patient had aneurysmal bleed. ‡Infection which was not present or suspected at the time of admission to the study. §Includes overt gastrointestinal bleed (haematemesis, bloodstained gastric aspirate or melena; and clinically important gastrointestinal bleed (overt gastrointestinal bleed with either, a fall in systolic blood pressure>20 mm Hg within 2 hours of bleeding; fall in haemoglobin >2 g/dl; blood pressure reduction >10 mm Hg; and increase in heart rate >20 beats/minute on orthostatic change; or need for blood transfusion). ¶Fasting sugar >160 mg/dl, requiring regular insulin in a patient who was not previously considered to have diabetes, and who was not receiving glucose.

Postpartum cerebral venous thrombosis, congenital protein C deficiency, and activated protein C resistance due to heterozygous factor V Leiden mutation

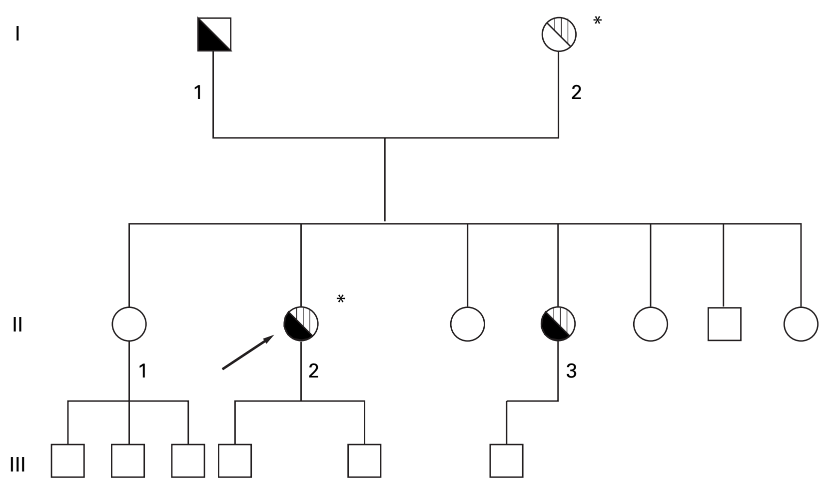
Activated protein C resistance (APC-R) due to factor V Leiden mutation is the most common thrombophilia associated with cerebral venous thrombosis. It is present in 10% to 20% of patients but usually in association with other constitutional or acquired prothrombotic conditions.[1] We present a case of postpartum cerebral venous thrombosis in a patient with protein C deficiency and APC-R due to heterozygous factor V Leiden mutation. In addition to puerperium, the role of intravenous steroids is questioned in this case.

A 33 year old woman was admitted because of severe subacute headaches, nausea, and drowsiness. She was not taking oral contraceptives. Her medical history disclosed recent delivery of a second child 3 weeks before and an asthma attack 5 days before entry, treated with intravenous methylprednisolone (120 mg daily). Family history disclosed that the patient's mother had had postpartum lower limb deep vein thrombosis. On admission, clinical examination disclosed papilloedema. There was no fever and no ear, nose, or throat infection. Brain CT showed a right temporal hypodensity, a delta sign, and small ventricles. Brain MRI (with MRA) demonstrated recent superior sagittal sinus, and right and left lateral sinus thrombosis. High dose intravenous heparin was immediately initiated. Heparin treatment was switched to warfarin after 10 days. At 3 months, neurological examination was normal. Follow up MRA showed complete recanalisation of the superior sagittal sinus and the right lateral sinus, and partial recanalisation of the left hypoplasic lateral sinus. Oral anticoagulation was maintained at International Normalized Ratio (INR) between 2 and 3). One year later, the patient is still symptom free under this treatment. The proband investigations were performed twice: during acute phase thrombosis and seven months later when the patient had temporarily discontinued oral anticoagulation therapy. Four other family members (the father, the mother, and two sisters) were available for examination (figure and table). The proband (II.2) exhibited qualitative protein C deficiency and APC-R due to heterozygous factor V Leiden mutation. Protein S activity and antithrombin III concentrations were normal. Search for antinuclear antibodies, anticardiolipin antibodies, and lupus anticoagulant, dysfibrinogenaemia, or plasminogen deficiency was negative. Plasma homocysteine concentration was normal. The father (I.1) had APC-R due to heterozygous factor V Leiden mutation. The mother (I.2) had a qualitative protein C deficiency. The first sister (I.1) had no APC-R nor protein C deficiency. The second sister (II.3), who had one pregnancy without any thrombotic event, had both protein C deficiency and APC-R due to heterozygous factor V Leiden mutation.

Our patient presented an extensive postpartum cerebral venous thrombosis with a double inherited coagulation defect: protein C deficiency and APC-R due to heterozygous factor V Leiden mutation. To our knowledge, the coexistence of these two thrombophilias has not been previously described in a patient with cerebral venous thrombosis. Genetic study showed that APC-R due to factor V Leiden mutation was transmitted by the patient's father and that protein C deficiency was transmitted by the patient's mother.

The protein C anticoagulant pathway is triggered when thrombin binds to the endothelial cell receptor thrombomodulin. This interaction converts thrombin into a potent protein C activator while blocking the fibrinogen clotting and platelet activating activity of thrombin. Activated protein C then serves as an anticoagulant by inactivating factors Va and VIIIa.[2] In our patient, acquired causes of protein C deficiency could be excluded. We diagnosed a congenital protein C deficiency with an autosomal dominant mode of inheritance. A type I deficiency could be postulated according to the reduction of both antigen concentration and activity of protein C, reduction of activity but normal antigen concentration being present in type II. Only a few cases of cerebral venous thrombosis with congenital protein C deficiency have been reported so far.[3,4] Inherited protein C deficiency seemed to be the sole risk factor for thrombosis in some cases[4] whereas other prothrombotic conditions such as the postpartum period were present in other cases.[3] Additional risk factors for thrombosis might be necessary for thrombotic manifestations to appear in patients with protein C deficiency as the heterozygous state is usually asymptomatic with an estimated prevalence of 1 in 200 to 300.[4]

In 1993, Dahlbäck *et al* described a new pathological condition termed APC-R, characterised by a poor anticoagulant response to activated protein C. This coagulation disorder is often associated with a single point mutation in one or both alleles of the factor V gene (adenine substituted for guanine at nucleotide 1691, the so called Leiden mutation) at a site of cleavage by activated protein C which delays inactivation of coagulant factor Va. The prevalence of the factor V Leiden mutation varies by geography and ethnicity, ranging from 2% to 15% in healthy white people. Factor V Leiden mutation is inherited as an autosomal dominant trait and most heterozygous people do not have clinical thrombotic complications. The odds ratio for venous thrombosis has been calculated to be 3.8-fold for heterozygous patients.[5] An important similarity of patients with APC-R and cerebral venous thrombosis is the frequency of other associated risk factors for thrombosis. Sixteen of 18 reported cases showed another genetic or acquired thrombosis risk factor: oral contraceptives in eight, pregnancy/puerperium in four, nephrotic syndrome in one, intravenous steroids in one, immobilisation in one, primary antiphospholipid antibody syndrome in one, and antithrombin III deficiency in one[1] These data suggest that the association of APC-R with an other prothrombotic state is crucial in the occurrence of cerebral venous thrombosis. In our patient, APC-R was associated with congenital protein C deficiency and two other acquired prothrombotic risk factors, postpartum and intravenous steroid therapy. The prothrombotic risk of intravenous steroids is questioned in our patient as she had not experienced any thrombotic event during her first pregnancy and postpartum period. It is noticeable that the patient's sister (II.3) with APC-R and protein C deficiency had had one child without venous thrombosis. The prothrombotic risk of intravenous steroids should be considered in patients with



*Pedigree of the family. The three generations are indicated by roman numbers. Arabic numbers indicate the family members who have been investigated. Square=male; circle=female; no deficiency open; protein C deficiency hatched; factor V Leiden black; *positive thromboembolism history . The proband is indicated by an arrow.*

Biological data of the proband (II.2) and her family

Patient	*Sex*	*Age*	*VT*	*FVL*	*APC-NR*	*PC (%)* *Coag*	*Chrom*	*Ag*
I.1	M	69	No	Yes	0.55	84	ND	ND
I.2	F	66	Yes	No	0.83	50	57	56
II.1	F	37	No	No	0.82	101	ND	ND
II.2*	F	33	Yes	Yes	0.53	61	68	78
II.2**		35			0.60	32	39	38
II.3	F	31	No	Yes	0.51	35	45	52
Normal values					>0.82	>70	>70	>70

VT=venous thrombosis; FVL=Leiden factor V; APC-NR=activated protein C resistance normalized ratio; PC=protein C; Coag=coagulant activity; Chrom=chromogenic activity; Ag=antigen; ND=not done; *II.2 proband coagulation screening during acute phase thrombosis; ** seven months later, without oral anticoagulant treatment.

APC-R. This case report also points out that the presence of APC-R should not delay the search for other causes in patients with cerebral venous thrombosis. The detection of single or multiple inherited coagulation defects has major practical consequences for the secondary prevention of these patients and for the primary prevention of the other family members, as these abnormalities usually have an autosomal dominant inheritance pattern. Long term management to prevent further venous thrombotic events in patients with isolated APC-R is not well delineated up to now, particularly regarding the duration of anticoagulation. Patients with combinations of APC-R and protein C or protein S deficiency have a higher risk of thrombosis than those with APC-R alone.[1 5] Lifelong oral anticoagulation may be advocated in patients with cerebral venous thrombosis and multiple inherited coagulation defects, such as protein C deficiency and APC-R.

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Intravenous immunoglobulin dependent inflammatory radiculopathy presenting as lumbar canal stenosis

A patient with symptoms and signs of lumbar canal stenosis showed non-malignant, nerve root hypertrophy on MRI. The patient responded dramatically but temporarily to intravenous immunoglobulin (IVIg).

Hypertrophy of nerve roots is recognised as a cause of "spinal stenosis" syndrome.[1] The association has been previously described with hereditary causes such as neurofibromatosis, Refsum's disease, and hereditary motor and sensory neuropathy (HSMN) type 1 and 3.[2] There have been recent reports of chronic inflammatory demyelinating polyneuropathy (CIDP) presenting as a spinal stenosis syndrome.[1 3] We report on a patient with an acquired inflammatory radiculopathy who presented with a lumbar canal stenosis syndrome only responsive to IVIg.

A 60 year old white man presented with a 2 year history of progressive numbness and stiffness of his legs with difficulty in walking. He had noticed the discomfort in his legs to be exacerbated after walking 100 metres and relieved by rest. He could cycle long distances without discomfort. He specifically denied any upper limb symptoms or sphincter disturbance. He had mild hypertension treated with nifedipine. There was no relevant family history.

Examination of the cranial nerves and upper limbs was normal. In the lower limbs there was symmetric wasting of the extensor digitorum brevis with grade 4/5 weakness of ankle dorsiflexion, eversion, and big toe extensors. Deep tendon reflexes were absent in the lower limbs. The plantar responses were flexor. Sensory examination disclosed pin prick, soft touch, and vibration sense to be reduced to knee level. Joint position sense was preserved.

Routine haematological and biochemical investigations were normal and there was no serum paraprotein. Prostate specific antigen, vitamin B_{12}, venereal laboratory research test, and HIV serology were negative. Enzyme linked immunosorbent assay (ELISA) Ig for *Burgdorferi* was negative. Plain radiology of the chest and lumbar sacral spine was normal. Intial CSF examination disclosed a raised protein of 2.08 g/l, glucose 3.7 mmol/l, and a white cell count of 40 cells/mm^3 (75% reactive lymphocytes). Cytology was normal. CSF angiotensin converting enzyme concentration was normal and acid fast bacilli culture negative. Nerve conduction studies and EMG showed dispersed F wave responses (right common peroneal 49–88 ms and right posterior tibial nerve 45–80 ms) together with denervation in the right tibialis anterior. Motor conduction velocities in the limbs were normal with preserved sensory action potentials. Lumbar spine MRI showed poorly defined hypertrophic nerve roots (figure).

On exploration of the intradural contents , the roots were "matted together" and not free floating in the CSF. Biopsies were taken of the ligamentum flavum, dura, and arachnoid, and this showed a mixed population of inflammatory cells in the ligamentum flavum sections. Examination of CSF on this occasion showed the same protein concentration of 2.08 g/l and a white cell count of 2 cells/mm^3.

Oral prednisolone (40 mg/day) caused a deterioration in his symptoms. The patient was given a 5 day course of IVIg (0.4 g/kg/day) and made a dramatic recovery and within 3 days the motor and sensory examination was normal but the knee and ankle jerks were still absent. Treatment with IVIg provides clinical benefit lasting 2–3 weeks, and neither this pattern nor the dose of IVIg prescribed has been altered by giving azathioprine, cyclophosphamide, or cyclosporin.

The patient presented with an acquired, non-malignant, root hypertrophy. There are electrical features to suggest this may be a CIDP, although the reactive CSF showed a higher white cell count than usual,[4 5] subsequent CSF white cell counts have been normal. Unlike previous cases of CIDP the root hypertrophy described in our patient has

MRI of the lumbar spine showing ill defined hypertrophic nerve roots (black arrow).

shown no benefit after oral immunosuppression. Indeed, introduction of a moderately high dose of prednisolone caused a dramatic deterioration, a response that is recognised in CIDP.[3 6] Unlike the modest clinical benefit seen by others after the adminstration of IVIg[3] our patient remains exquisitely sensitive to IVIg.

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Sodium valproate for tinnitus

In 1935 Barany serendipitously discovered the temporary relief of tinnitus after lignocaine injection of nasal turbinates.[1] Since that time, other agents known to suppress the activity of excitable membranes have been tried, including antiarrhythmic and anticonvulsant drugs. Among such drugs, carbamazepine has the best documented efficacy in patients with a positive lignocaine test,[2] but is generally unhelpful in unselected tinnitus populations and often discontinued due to adverse effects.[2 3]

A 53 year old man with viral cardiomyopathy developed severe (60 dB) tinnitus after bilateral temporal lobe strokes. Various treatments including masking and diazepam were unhelpful. Carbamazepine (200 mg nightly) was effective, but was withdrawn due to progressive hyponatraemia (120 mM after two weeks of therapy), followed by the rapid recurrence of tinnitus. Sodium valproate (200 mg twice daily) was also promptly effective in suppressing tinnitus, and was well tolerated until his death due to cardiac arrhythmia one month later.

In part due to its diverse aetiology, pharmacotherapy of tinnitus has met with very limited success.[2 4] Uncontrolled trials in the French[3] and Japanese[5] literature have indicated benefit from sodium valproate in selected patients, but its use seems not to have been described in English apart from a specialist monograph.[2] Tinnitus loudness[5] and sensorineural pathology[3] but not lignocaine response[5] seem to predict response. Valproate may also differ from carbamazepine in that it seems better tolerated in an unselected tinnitus population.[3] Controlled studies of valproate for this common, often debilitating[4] condition seem warranted.

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Audible carotid dissection

Carotid dissection is a common cause of stroke in the young patient and can present with various clinical syndromes or symptoms. These may include stroke or transient ischaemic attack,[1] ipsilateral ptosis, isolated or multiple cranial nerve palsies,[2] carotidynia, hemicrania,[3] scintillating scotomata, pulsatile tinnitus, or subjective bruit.[4] I recently cared for a man who experienced an audible "creaking" sound heard even by his wife in the hours before a right middle carotid artery (MCA) infarct secondary to a carotid dissection. I think that this sound represented the actual dissection.

A forty three year old, right handed lawyer with a presumed viral pharyngitis and severe cough for two weeks duration returned from work at 6 00 pm and began hearing periodic, high frequency, "creaking" sounds in his right ear. These sounds occurred every 1–2 hours lasting a few seconds each time. These sounds were not pulsatile or rhythmic. He had not experienced these sounds previously with his illness. When sitting at the dinner table, his wife too heard these peculiar sounds. On admission she provided a detailed description of these sounds as the patient himself was lethargic. At midnight, he experienced a scintillating scotomata with right retroorbital headache and by 1 30 am was lethargic with a left sided weakness. According to the wife and the patient these sounds had now ceased and did not recur.

On examination he had diminished attention, and mental status was otherwise normal. Neck auscultation was normal and there was no audible creaking sound. Fundi and visual fields were normal. A left lower facial droop was present with otherwise normal cranial nerve function. Left arm plegia and left leg paresis was present with associated hyperreflexia and extensor plantar response. He reported diminished sensation to pin, position, and light touch and extinguished left sided touch on simultaneous bilateral stimulation. Brain MRI at 12 hours showed a T1 hypointense and T2 hyperintense lesion in the anterior MCA distribution, thrombus in the MCA (M-1 segment), with a suggestion of focal narrowing in the upper cervical region of the right internal carotid on MRA. An angiogram confirmed a right internal carotid dissection and MCA thrombus. The patient was anticoagulated and with rehabilitation is ambulatory with partial use of his left arm.

Whereas the clinical picture may be typical of carotid dissection, the clearly audible creaking sound that occurred in the early phase of the illness was unusual. I excluded relating this sound to middle ear congestion, hallucinosis, or aura of migraine or epilepsy as these possibilities would have been subjective phenomena not experienced by the patient's spouse. More commonly, auditory symptoms associated with carotid or vertebral dissection are related to altered vascular haemodynamics. Subjective sudden onset of bruit and pulsatile tinnitus are well described and are relatively frequent symptoms of carotid dissection. When present, these symptoms are constant, occasionally appreciated by auscultation, and usually persist even after presentation to the physician. Again however, to my knowledge they have not been reported as being heard externally. Aortic dissection can have a variable presentation, but I have been unable to find evidence of externally heard sounds in this setting.[5]

I suggest that these audible creakings in the context of a later documented arterial dissection were more likely the early tearing sounds themselves of the carotid dissection evolving over several hours. Such sound could have been heard externally and would have represented a progressively enlarging mechanical tear of a high pressure arterial system. The fact that these sounds were intermittent and recurrent, of limited duration, and unassociated with complaints of bruit or tinnitus suggests that the dissection developed slowly with several short bursts of "mini-dissection" before the devastating stroke. This case offers additional evidence that some carotid dissections may have a time course that if recognised might be amenable to emergency intervention. If a patient reports audible creaking without a clear explanation, an evolving arterial dissection should be considered.

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Gynaecomastia in association with phenytoin and zonisamide in a patient having a CYP2C subfamily mutation

Anticonvulsant drugs can have various side effects on endocrine functions, such as impotence, hirsutism, infertility, and thyroid dysfunction. Gynaecomastia is caused by many types of drugs such as methyldopa, tricyclic antidepressant drugs, isoniazid, and spironolactone,[1] but there have been only a few reports of gynaecomastia caused by anticonvulsant drugs, including phenytoin[2] and zonisamide.[3] We recently encountered a young man with partial seizures, who genetically had a heterozygous mutation of both CYP2C9 and CYP2C19,[4] normally responsible for biotransformation of phenytoin in the human liver microsomal *P*-450 system.[5] He developed gynaecomastia after increasing the dose of phenytoin.

The patient was an 18 year old man with a diagnosis of left parietofrontal lobe epilepsy since the age of 2 years, until which time his developmental milestones were normal. He had complex partial seizures occurring at least once every day despite various anticonvulsant drugs of usually sufficient dose including clorazepate, phenytoin, and carbamazepine, and zonisamide since the age of 9 years, when he had an epilepsy surgery for a focal high intensity abnormality on T2 weighted MRI in the left parieto-occipital area.His seizures were not controlled. At the age of 18 years, the patient had chronic implantation of subdural electrodes for evaluating the intractable seizures, and based on the results of the invasive evaluation, he had focal resection in the left parietal and mesial parietofrontal areas. After surgery his seizures decreased in frequency to once every week, and became less severe, accompanied by loss of awareness in only a third. Before and after the surgery he was taking phenytoin (175 mg/ day), carbamazepine (900 mg/day), and zonisamide (400 mg/day) giving blood concentrations of 14.3 mg/l, 7.9 mg/l, and 13.2 mg/l, respectively. Two months after surgery, partly because of sleep deprivation, the patient had a cluster of complex partial seizures, some resulting in secondary generalisation, occurring seven times in 90 minutes. After a total of 375 mg phenytoin was intravenously loaded, his seizures were well controlled. Subsequently the medication was maintained at phenytoin (190 mg/ day), carbamazepine (1100 mg/day), and zonisamide (400 mg/day), and the steady state, basal blood concentrations of these anticonvulsant drugs were 16.6 mg/l, 5.2 mg/l, and 9.7 mg/l respectively.

About a month later, the patient noticed bilateral enlargement of his breasts associated with some tenderness restricted to the centre of the breast. The size was about 3 cm in diameter. No galactorrhea was seen. Blood concentrations of luteinising hormone, follicle stimulating hormone, prolactin, and oestradiol were all normal. His liver function was also within normal limits except for slight increases in γ-GTP. The patient had had moderate gingival hypertrophy and mild hypertrichosis. He was taking no medication other than the anticonvulsant drugs.

On rare occasions gynaecomastia has been reported in patients taking phenytoin, and in some of them it disappeared after stopping phenytoin.[2] The mechanism as to how gynaecomastia is caused by this drug is uncertain. It was pointed out that some drugs interfere with testosterone synthesis as well as action by blocking the cytosol receptor of androgen in target tissues. Is has been shown that liver enzyme inducing antiepileptic drugs such as carbamazepine and phenytoin are associated with increased concentrations of serum sex hormone binding globulin and decreased amounts of free androgen available in the tissue.[6] However, as for most drugs causing gynaecomastia, its mechanism is not well defined.

The anticonvulsive drug zonisamide has been clinically available in Japan for patients with seizures since 1989, and it is reported that three patients (age ranging from 3 years to 32 years) taking zonisamide (60 to 600 mg/day) developed gynaecomastia from 10 days to 1 year after taking zonisamide, and in all of them it disappeared after stopping zonisamide.[3] Therefore, in the present patient, it is possible that both phenytoin and zonisamide played important parts in the development of gynaecomastia. However, the patient had been on zonisamide for the past 8 years, and its dosage was not increased before gynaecomastia developed. On the other hand, after phenytoin was loaded when he had frequent seizures, its maintenance dosage increased. Therefore, phenytoin is most likely a causative agent. Adolescent gynaecomastia usually occurs bilaterally, although asymmetric, in many boys as a physiological type, often during puberty with a mean onset age of 14 years, and it is correlated with transiently raised oestradiol of unknown origin before completion of puberty.[1] However, there was no increase in oestradiol in the present patient.

The patient had a heterozygous point mutation in the defective allele of CYP2C9 and CYP2C19,[4] and in such patients V_{max} values in the pharmacokinetics of phenytoin were 40% lower than those in patients with a normal type CYP2C subfamily (see subject No 43 in fig 1 of Odani *et al*[4]) and thus our patient's maintenance dose of phenytoin (175 mg/ day) was relatively small to achieve an appropriate blood concentration (14.3 mg/l). After having increased the maintenance dose of phenytoin by 15 mg/ day, the blood concentration was kept <20 mg/l, and clinically he did not show toxic symptoms such as cerebellar ataxia and gaze evoked nystagmus. The presence of a heterozygous CYP2C subfamily mutation might have played some additional part either in developing this rare side effect or in facilitating physiological gynaecomastia of the adolescent type.

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Neuropsychological prediction of dementia in Parkinson's disease

Mahieux *et al*[1] report on an interesting study of predictors of dementia in Parkinson's disease. We have certain reservations about the results because of the methodological limitations of the study.

The diagnosis of dementia was made by retrospective case note review or retrospective completion of questionnaires including some by non-specialists which raises questions about the validity of diagnosis. The researchers making the diagnosis of dementia were not blind to neuropsychological test score, which raises the possibility of observer bias. The study was uncontrolled so that the estimate of the incidence of dementia cannot be adequately interpreted because it is not known what the incidence in the general population would be using this method of case identification.

The findings of predictors of dementia are a little puzzling. Aithough four variables are reported as predictors, this seems to be misleading because for all but one of these the 95% confidence interval for the relative risk includes the figure one, indicating that the relative risk is not significant at the 5% level using a hypothesis test.[2] The p values for two of these variables were indeed greater than 0.05, but although the p value is given for the WAIS picture completion subtest as 0.03 (table 3, not table 2 as stated), the 95% confidence interval for the relative risk includes one. If these two statistical tests give different answers, which is correct?

For only one predictor variable did the 95% confidence interval of the relative risk lie outside one. This variable, age at onset of Parkinson's disease, was entered into the multivariate model, but it seems that age at inception to the study was not entered into the model. It is well known that dementia in Parkinson's disease is associated with age.[3 4] If age onset is correlated with age at entry to the study as has been found by others[3 5] then age at onset of Parkinson's disease is confounded. Many studies have reported that dementia in Parkinson's disease is associated with older age at onset, but those studies which have controlled for the effect of age have not found such an association.[5 6]

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3 Ebmeier KP, Calder SA, Crawford JR, *et al*. Clinical features predicting dementia in idiopathic Parkinson's disease: a follow-up study. *Neurology* 1990;**40**:1222–4.
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The authors reply:

We appreciate the interest of Hughes *et al* in our study on the neuropsychological prediction of dementia in Parkinson's disease.[1]

The validity of the diagnosis of dementia was discussed in the paper. Hughes *et al* conjecture that the knowledge of initial neuropsychological tests scores would raise an observer bias. But the final diagnosis (dementia or not) was made by independent raters in 22 cases out of 86, and in every case we used a special case report form which did not even refer to the initial neuropsychological examination.

We agree that the incidence of dementia in our population cannot be interpreted as that of an inpopulation epidemiological study. We mentioned it as a mere additional descriptive characteristic.

We agree that the significance of the completion subtest was borderline in the multivariate analysis, as the confidence interval of the relative risk includes one, according to the calculation done by BMDP software. The level of significance is < 0.05, as mentioned in the table, again according to the test performed by the BMDP package. This minor discrepancy is not unusual and should not affect the interpretation of our results in such an exploratory clinical epidemiological study.

With regard to age and age at onset, these two variables correlate strongly. The two have been reported as predictive factors for dementia in Parkinson's disease.[2–5] Some authors consider that age at onset of Parkinson's disease is a potentially more important variable.[5–7] Moreover, the inclusion of age instead of age at onset in the multivariate analysis modifies the results only slightly. The WAIS-R completion subtest and age remain significant and independent predictors of dementia with respective risk ratios of 5.344 for age>68 years (95% CI 1.7–17.1; $p<0.01$) and 10.929 for a completion score <10 (95% CI 2.5—48.3).

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Repeated syncopes and extended paediatric hydrosyringomyelia/Chiari I malformation

I have read with interest the letter recently published on *Repeated syncopes and extended paediatric hydrosyringomyelia/Chiari I malformation*.[1] The case reported is quite unusual, as syncope seems to be a very rare manifestation of this condition, even when associated with a Chiari malformation, at least in adults. From a series of 100 adult patients with syringomyelia diagnosed over the past 10 years at this institute, two thirds of whom had an associated Chiari type I anomaly, only one patient had syncope, which was triggered by sneezing. Another three patients had drop attacks without loss of consciousness, one with a Chiari type I anomaly, and two with an associated ventricular dilatation (figure).

In the paper mentioned by the authors on cardiovascular reflexes in syringomyelia,[2] all patients with autonomic involvement, even those without syringobulbia, had an abnormal neurological examination, and sweating abnormalities and Horner's syndrome were often encountered. The fact that neurological examination was normal in the patient described by Woelfle *et al*,[1] as well as the absence of Horner syndrome and sweating abnormalities, make autonomic dysfunction an unlikely explanation for the episodes described, although it may be a contributing factor. As syncope was associated with occipital headaches, transient brainstem compression may play a significant part. As the authors suggest, the precise mechanism of these episodes and of drop attacks is difficult to determine, and they may be multifactorial.

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MRI of a 50 year old woman with syringomyelia, Noonan's syndrome, and frequent drop attacks. There is a cervical syrinx and moderate dilatation of the fourth ventricle. There is no Chiari anomaly.

1 Woelfle J, Haverkamp F, Kreft B. Repeated syncopes and extended paediatric hydrosyringomyelia/Chiari I malformation: relation or coincidence? *J Neurol Neurosurg Psychiatry* 1998;**64**:278–9.
2 Nogués MA, Newman PK, Male W, *et al*. Cardiovascular reflexes in syringomyelia. *Brain* 1982;**105**:835–49.

The authors reply:

As Nogues mentions, the association of hydrosyringomyelia and syncope is a very rare event. To our knowledge, our patient is the first child reported demonstrating such a clinical picture.[1] In his opinion, the normal neurological examination in our patient makes autonomic dysfunction as the underlying mechanism of the repeated syncopes unlikely. Considering the association of syncope with occipital headache, he suggests that transient brainstem compression may be a causal factor in the mechanism leading to syncope. However, the association of headache was not a consistent finding in all of the five noted syncopal events in our patient. Furthermore, hydrosyringomyelia usually remains asymptomatic in childhood,[2] indicating a time dependent degree of damage to the spinal cord. Thus, in our opinion a normal neurological status in children does not necessarily exclude temporary dysfunction of the sympathetic system, assuming that temporary, preclinical damage to the spinal cord in childhood may well progress to permanent autonomic dysfunction in adulthood. In addition, even in adults with some symptoms of autonomic dysfunction, the lesion of autonomic outflow paths in the spinal cord may be incomplete, with absence of Horner's syndrome and preservation of some autonomic reflexes.[3] In our patient, autonomic dysfunction was supposed to be the most likely mechanism due to the pattern of affected syringomyelic areas in combination with the finding of impaired cardiovascular reflexes in adults with hydrosyringomyelia, in whom longstanding pressure changes may have led to permanent, irreversible destruction of autonomic structures in the medulla.[4]

Of course, we are well aware that all the theoretical models outlined in our case report, even the causal relation between syncope and hydrosyringomyelia/Chiari I malformation, remain speculative and neither his nor our theory can be proved. We agree with Nogues, that probably syncopes and drop attacks in these patients are of multifactorial origin with various possible contributing factors including neurological, cardiovascular, and neuropsychological influences.

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1 Woelfle J, Haverkamp F, Kreft B. Repeated syncopes and extended paediatric hydrosyringomyelia/Chiari I malformation: relationship or coincidence ? *J Neurol Neurosurg Psychiatry* 1998;**64**:278–9.
2 Logue V, Edwards MR. Syringomyelia and 1st surgical treatment - an analysis of 75 patients. *J Neurol Neurosurg Psychiatry* 1981;**44**:273–84.
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4 Nogues MA, Newman PK, Male VJ, *et al*. Cardiovascular reflexes in syringomyelia. *Brain* 1982;**105**:835–49.

BOOK REVIEWS

Diseases of the Nervous System in Childhood. Second edition. Edited by JEAN AICARDI. (Pp900, £150.00). Published by Cambridge University Press, Cambridge, 1998. ISBN 1-898683-16-6.

In the first edition of this text in 1992 Professor Aicardi argues for the continuing role of clinical history and examination in the face of rapidly advancing techniques of neuroimaging and neurophysiology. In his preface to the second edition he describes the need for someone to marshall and make sense of the deluge of information available in a world in which only computerised networks can keep pace with new developments and new data in medical sciences. The experience in the field of childhood neurology of Professor Aicardi and his coauthors enables the organisation of this volume of information, and the direction of the reader to the most important and significant data. This second edition succeeds in its aim to incorporate the major developments of the past 6 years and provide an access route to further information in the literature, while retaining the overall outline of the first edition. The book is primarily clinically oriented, comprehensively describing the neurological diseases of childhood in sufficient detail to enable diagnosis, prognosis, and management. It will be of value to all physicians with an interest in childhood neurological disorders, including general paediatricians, neurologists, and other physicians interested in developmental medicine. The book is divided into 11 main sections, covering childhood neurology from fetal development through to developmental and neuropsychiatric disorders of older children and adolescents. This last section is written by Professor Gillberg from Goteburg and is prefaced by a succinct and very useful chapter on normal mental and behavioural development. For the section on cerebral palsy Professor Aicardi is joined by Martin Bax and they note the lack of longitudinal data on the natural history of cerebral palsy, unfortunately a common problem in paediatric neurological disorders, together with a lack of randomised controlled trials of therapies. The chapter on metabolic diseases is co written with Helene Ogier from Paris and this area of increasing importance is very clearly presented and illustrated. Otherwise the book is single author and extensively referenced, with an emphasis on recent articles. It is well illustrated, particularly with high quality neuroimaging reproductions. The numerous tables are comprehensive and of great practical use to the physician attempting to construct a differential for obscure diagnoses. This book is one of the best of its kind and, as with the first edition, will continue to take first place on the bookshelf of all paediatric neurologists. It is also highly readable and will remain the "friendly companion even at the bedside" that Professor Aicardi aims for, a role not yet overtaken by computer technology.

LOUISE HARTLEY

The Molecular and Genetic Basis of Neurological Disease. Second edition. Edited by ROGER N ROSENBERG, STANLEY B PRUSINER, SALVATORE DI MAURO, AND ROBERT L BARCHI. (Pp 1430). Published by Heinemann, Oxford, 1997. ISBN 0-7506-9668-0.

This book is well known to many neurologists and represents the foremost book for this area of neurological practice. The latest edition is dedicated to the life and accomplishments of the late professor Anita Harding and serves as a very fitting tribute to this remarkable neurologist.

The book is divided into 23 sections and contains nearly 1500 pages of text in the form of 77 chapters. It is therefore impossible to do justice to a book of this nature in a short book review, but for detail and clarity, there are few books to compete with this tome. The book opens with an account of some of the more general issues in genetics which is especially helpful for the non-specialist as it helps explain the approach in tackling neurological disorders from a genetic point of view. Indeed, this is ultimately the problem with a book of this type, in that the field moves forward with such speed that chapters soon become out of date. For example, the chapter on Huntington's disease does not discuss recent animal models of this disease using expanded CAG repeats and the significance of intranuclear inclusion bodies.

Furthermore, whereas the expanded triplet repeat in Friedreich's ataxia is well discussed, no details are presented on the role of frataxin. These, however, are minor points in what is clearly an excellent reference book. Each condition is concisely documented with good illustrations and up to date reference lists, and thus readers can easily remind themselves about various conditions. There are occasional omissions—for example Pelizeus-Merzbacher disease does not appear in this book even though the genetics of this conditions are now becoming clearer.

This book is a must for all libraries but from an individual point of view it may seem extravagant to own a copy especially in a field that moves so fast. Specialists in neurological genetics would probably want to own a copy and update it manually as new information emerges. For the more general neurologist, a large neurological textbook probably offers a better buy as it covers all the conditions in this book and more. However, I loved this book and enjoyed dipping into it to catch up on the latest developments in the ever increasing array of neurogenetic disorders. Although many of these disorders are still rare, it seems that more and more neurological conditions will be found to have a genetic basis, and so an understanding of genetics, especially at the molecular level, will be an essential part of any neurologist's training. So why not start now with this book?

ROGER BARKER

Neuroimaging and the Psychiatry of Late Life. Edited by DAVID AMES AND EDMOND CHIU. (Pp242). Published, by Cambridge University Press, Cambridge, 1997. ISBN 0-521 49505 9.

The continuing rapid expansion of neuroradiology, with new technologies and improvements in more well established techniques, have sharpened the tools with which to examine neurological and psychiatric diseases of old age. Investigation of, for example, the MRI findings in vascular dementia and depression, measurements of medial temporal lobe structures in Alzheimer's disease, and functional imaging studies of schizophrenia, have led to new insights into the diagnosis, prognosis, and symptomatology of these ill understood diseases. However, there are two obstacles in the understanding of this expanding area of research for the interested neurologist and psychiatrist—namely, understanding of the basis of the technology and relating the research findings to best clinical practice. The remit of this text covers both these deficiencies.

For the non-physicist getting to grips with the basic principles and methodologies of neuroimaging can be daunting. The first section of this book explains the basic principles behind the hardware of the imaging department and this is aided by many excellent diagrams. The general clinical indications and safety issues of structural (CT and MRI) and functional (PET, SPECT and EEG) imaging techniques are well reviewed and illustrated.

The second section of the text explores the research questions and summarises the answers so far in the field of old age psychiatry. Interpretation of imaging research in abnormal elderly patients, with regard to subject selection, imaging technique and the relation to normal aging, is one of the main dilemmas in this field. This is fully discussed in the admirable chapter on normal aging, which commences this review of the research. Other chapters on Alzheimer's disease, vascular dementia, other dementias, delirum, affective disorders, and schizophrenia of late onset continue this well referenced text. Besides presenting the data for the clinican, this comprehensive review will also be appreciated by researchers in this field.

The third part of this book returns to the application of these results to clinical practice. Both an American and European perspective on the clinical interpretations of the above data are presented and the conclusion can be quoted "Our ability to image the brain, however, has in some cases outpaced our ability to understand the clinical implications of the structural and functional findings seen using modern imaging techniques". In other words this interesting research which has been so excellently summarised here has yet to make an real impact on routine clinical practice.

CLARE GALTON